Effects of Treatment on Outcome in Mildly Symptomatic Patients With Ischemia During Daily Life

The Atenolol Silent Ischemia Study (ASIST)

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Background Detection of asymptomatic ischemia in patients with coronary artery disease has been associated with increased risk for adverse outcome, but treatment of patients with asymptomatic ischemia remains controversial. Accordingly, the purpose of this study was to determine if treatment reduces adverse outcome in patients with daily life ischemia.

Methods and Results A multicenter, randomized, double-blind, placebo-controlled study of asymptomatic or minimally symptomatic outpatients with daily life silent ischemia due to coronary artery disease was conducted. The primary outcome measure was event-free survival at 1 year by Kaplan-Meier analysis. Events were death, resuscitated ventricular tachycardia/fibrillation, myocardial infarction, hospitalization for unstable angina, aggravation of angina, or revascularization. The secondary outcome was ischemia during ambulatory ECG monitoring at 4 weeks. Three hundred six outpatients with mild or no angina (Canadian Cardiovascular Society class I or II), abnormal exercise tests, and ischemia on ambulatory monitoring were randomized to receive either atenolol (100 mg/d) or placebo. After 4 weeks of treatment, the number (mean±SD, 3.6±4.2 versus 1.7±4.6 episodes, P<.001) and average duration (30±3.3 versus 16.4±6.7 minutes, P<.001) of ischemic episodes per 48 hours of ambulatory monitoring decreased in atenolol- compared with placebo-assigned patients (4.4±4.6 to 3.1±6.0 episodes and 36.6±4.1 to 30±5.5 minutes). Event-free survival improved in atenolol-treated patients (P<.0066), who had an increased time to onset of first adverse event (120 versus 79 days) and fewer total first events compared with placebo (relative risk, 0.44; 95% confidence intervals, 0.26 to 0.75; P=.01). There was a nonsignificant trend for fewer serious events (death, resuscitation from ventricular tachycardia/fibrillation, nonfatal myocardial infarction, or hospitalization for unstable angina) in atenolol-treated patients (relative risk, 0.55; 95% confidence intervals, 0.22 to 1.33; P=.75). The most powerful univariate and multivariate correlate of event-free survival was absence of ischemia on ambulatory monitoring at 4 weeks. Side effects were mild and generally similar comparing atenolol- and placebo-treated patients, although bradycardia was more frequent with atenolol.

Conclusions Atenolol treatment reduced daily life ischemia and was associated with reduced risk for adverse outcome in asymptomatic and mildly symptomatic patients compared with placebo. (Circulation. 1994;90:762-768.)

Key Words • ischemia • coronary disease • atenolol

It is generally accepted that the presence of myocardial ischemia is associated with an increased risk of untoward events in patients with coronary artery disease (CAD). Recently, numerous studies have focused on the most common form of ischemia, asymptomatic or silent ischemia, identified during routine daily life by ambulatory electrocardiogram (AECG) monitoring.1-3 In many studies, patients with AECG-detected ischemia have had an increased risk for adverse outcome compared with patients without AECG-monitored ischemia.4-22 Anti-ischemic treatment is frequently used in such patients, but no prospective controlled studies of anti-ischemic treatment have been published to address whether treatment of patients with ischemia during daily life is associated with reduced risk of adverse outcome.

To test the hypothesis that anti-ischemic treatment would reduce the risk of adverse outcome among patients with asymptomatic ischemia during daily life, we conducted a prospective, randomized, double-blind study comparing the effects of an anti-ischemic agent (atenolol) with placebo. We enrolled only asymptomatic and minimally symptomatic patients (class I or II, Canadian Cardiovascular Society) in an attempt to focus on treatment given specifically for daily life ischemia rather than treatment required for symptom control.

Methods

This multicenter study was investigator initiated and designed (see “Appendix” for sites and principal investigators). Site initiation, special training in AECG monitoring, and patient recruitment commenced January 2, 1990, and the first patient qualified for entry on January 18, 1990. Briefly, after
screening (2 weeks), eligible patients entered a 2-week, single-blind, placebo period during which baseline history, physical examination, exercise testing (Bruce protocol), and AECG monitoring were done. Those meeting eligibility criteria were randomized, entered a double-blind, placebo-controlled treatment period and were followed until an end point was reached. The study was overseen by an executive steering committee chaired by an executive director responsible for the overall conduct of the study. The study was monitored by an independent data and safety monitoring committee (DSMC). The protocol was approved by the institutional review board at each participating site. Informed consent was obtained from each patient.

Eligibility
Potentially eligible patients were identified from those who had previously presented with CAD, and no attempt was made to screen the general asymptomatic population. To be eligible, patients of either sex and any age were required to have (1) documented CAD evidenced by either coronary angiography (>50% diameter stenosis of a major coronary artery) or a previously documented myocardial infarction and (2) transient ischemia evidenced by abnormalities during an exercise ECG (standard Bruce protocol). This 2-week baseline AECG (201-stripe) taken at each regional wall motion study done within 6 months of study entry. Patients who had ischemic abnormalities on two independent noninvasive tests (eg, exercise ECG ST-segment depression ≥1.0 mm plus stress thallium-201 redistribution abnormalities) were also considered to have evidence for CAD. Patients with any of the following were excluded: unstable angina pectoris, myocardial infarction, or coronary revascularization within 3 months of study entry; an ECG abnormality interfering with exercise or AECG ST-segment analysis; other serious condition (medical, psychiatric, cognitive, or social); symptoms of sufficient severity (Canadian class III or higher) to require antianginal medications other than nitrites; anticipated need for either β-blocker or calcium antagonist treatment; and heart failure, greater than first-degree atrioventricular block, asthma, or other contraindications to β-blockade therapy.

A real-time AECG system network was designed to deal with practical problems associated with large-scale, long-term AECG monitoring for multicenter trials. Each site was trained by the same workers, used the same equipment and instruction sheets, and was linked electronically with the AECG core laboratory facility. A detailed description of the system designed for this study appears elsewhere.

Briefly, this system allows for analog-to-digital conversion and ECG signal processing within the monitor (Monitor One Omni, Q-Med) in real time. AECG data were downloaded for rapid transmission by modem from the site, immediate confirmation of signal quality and lead position, objective analysis, physician overreading, and transmission of results to the site using a validated system for ST-segment and heart rate analysis. In addition, each qualifying patient’s baseline AECG lead pattern was stored and compared with follow-up AECG lead patterns to ensure that the leads were recording from the same position in each patient. Sites were blinded to all AECG data. No AECG results were available to the physicians or patients during the study. An ischemic episode was defined as a period of horizontal or downsloping ST-segment depression ≥1 mm, persisting ≥1 minute, and separated from another episode by ≥1 minute. To qualify for randomization, patients meeting entry criteria were required to demonstrate either two or more asymptomatic ischemic episodes or a single asymptomatic episode with a duration of ≥5 minutes during 48 hours of AECG monitoring in the placebo lead-in period.

Randomization and Treatment
At the end of the placebo lead-in period, patients meeting the above entry criteria were randomly assigned to receive either placebo or atenolol according to a computer-generated random code. Study investigators and patients were told to assume that they were taking atenolol and to conduct themselves accordingly. Study drugs (atenolol or matching placebo) were supplied (as Tenormin by ICI/Zeneca Pharmaceuticals) in 50- and 100-mg tablets. All patients were started at 100 mg daily, titratable to 50 mg should limiting side effects develop.

Follow-up
The patients were followed at 4, 15, 26, 39, and 52 weeks or whenever interim evaluations were required for symptoms, events, or side effects. At the 4-, 26-, and 52-week visits, AECG monitoring was done.

Assessment of Treatment Effect
The primary study outcome measure was event-free survival at 1 year. The following ischemia-related events were considered end points: death, resuscitation from ventricular tachycardia/fibrillation (VT/VF), nonfatal myocardial infarction, hospitalization for unstable angina, aggravation of angina requiring known antianginal therapy, and need for revascularization. All patients reaching end points and their supporting data (eg, ECGs and hospital records) were reviewed by the DSMC, and the classification of events was made by the DSMC.

The event that occurred first was considered the primary end point, so that if a patient developed unstable angina and was hospitalized and then while hospitalized developed a myocardial infarction and died, unstable angina was the primary end point for that patient. Myocardial infarction was considered an end point when a patient was hospitalized and infarction was documented by ECG and/or enzyme criteria without recognizable antecedent unstable angina. Unstable angina was used as an end point when the patient required hospitalization because the severity or the pattern of anginal pain had changed (eg, crescendo or rest) without documentation of myocardial infarction. All patients included in this category had clinical and ECG changes of ischemia without ECG or enzyme changes of infarction and were hospitalized before exiting the protocol. Aggravation of angina was used as an end point when the patient’s clinical picture had changed so that a 50% chance of placebo therapy was no longer acceptable. The patient required either medical therapy (eg, open-label antianginals) or revascularization treatment (eg, percutaneous transluminal coronary angioplasty [PTCA] or coronary artery bypass grafting, [CABG]). The patient in this category may require hospitalization for the actual intervention (catheterization, PTCA, or CABG) but not for the pattern of chest pain. Thus, for patients who developed new-onset or increased angina, were given known antianginal therapy, or were admitted for catheterization and then had CABG, this aggravation classification was used. Need for revascularization was used as an end point in the rare case that this intervention occurred in the absence of altered symptoms such as reinterpretation of a previous angiogram or the decision to undertake revascularization because of patient or physician choice despite lack of change in the clinical picture. The secondary measure of treatment effect was AECG monitoring of ischemia at 4 weeks.

Blinding to Treatment
Blinding to treatment was maintained by the executive coordinator, executive committee, the DSMC, study investigators and coordinators, and patients throughout both interim analyses. At the termination of the study, investigators and study nurses were told to assume that patients had been treated with atenolol and to consider replacement of study
medication with a known β-blocker in a dose comparable to that received during the study. This was done as an attempt to prevent possible β-blockade withdrawal phenomena.

**Statistical Analysis**

All analyses were performed on an intention-to-treat basis. Continuous variables were analyzed with unpaired t tests and categorical data by χ² tests, and all comparisons were two sided. Because a large number of baseline variables were compared, a value of P<.001 was considered significant for these comparisons. Kaplan-Meier analyses were used to examine the time-dependent cumulative probabilities of the outcomes. Relative risk ratios and 95% confidence intervals were calculated for reductions in risk. A multiple stepwise logistic regression model²⁷ was used to examine the predictive value of variables considered likely to have a clinically important association with 1-year outcome. All data were expressed as mean±SD of the mean or frequency when appropriate, and log transformation was used for duration of ischemia. In the analysis of the late follow-up AECG data, ischemia was considered present if an ischemic episode was recorded or an ischemia-related event had occurred.

It was planned that 350 patients (175 per treatment group) would be enrolled and that each patient would be followed for a minimum of 1 year or until an event occurred. This sample size was estimated to detect a 50% reduction in the combined risk for adverse outcomes at the .05 level of significance (two sided) and with a power of 0.90. From previous reports of patients with stable CAD who had abnormal exercise tests and AECG-monitored silent ischemia, the expected incidence of total cardiac events over 1 year was approximately 30%, using a linear model.⁴⁻⁵ Based on an estimate that patients will have approximately five ischemic episodes during 48 hours of AECG monitoring²⁶²⁹ during the lead-in, this sample size will allow detection of an absolute difference of approximately two in the average number of episodes.

Three interim analyses were planned, but only two were actually conducted. The first was done in March 1991 and the second on October 23, 1992. Based on results of the second analysis, showing a significant reduction in risk of adverse outcome in one treatment group, the DSMC recommended that the study be terminated early. The study was terminated on November 14, 1992.

**Results**

Two thousand thirty-seven patients were screened for participation. A total of 1368 patients with evidence for CAD and ischemia on stress testing underwent AECG monitoring. Seventy-six percent of these (1043 patients) were excluded after AECG monitor screening because of insufficient asymptomatic ischemia. Three hundred six (22.4%) qualified and were randomly assigned to either placebo (n=154) or atenolol (n=152) treatment.

The remainder (19 patients, 1.4%) either refused to continue or were excluded for miscellaneous reasons (eg, desire not to undergo repeated 48-hour AECG or unreliable with AECG equipment). The clinical characteristics and results of exercise testing in those patients randomized are summarized in Table 1. The mean age was 64 years in both treatment groups, and there was a similar number of elderly (≥65 years) patients in both groups. The patients were mostly men (84% in the placebo group and 90% in the atenolol group) and Caucasian (92%). The percentages of patients in each treatment group who were symptomatic during screening were similar, and the majority required no background nitrate therapy. There were no significant differences comparing baseline characteristics of the two treatment groups.

Exercise ECG data at baseline revealed that the heart rate achieved at onset of 1.0-mm ST-segment depression was 127±17 (mean±SD) and 126±17 beats per minute in the placebo and atenolol groups, respectively. There were no significant differences in heart rate, systolic or diastolic blood pressures, or exercise time at onset ischemia comparing the two groups.

The average heart rate was 75.1±12.9 beats per minute, and there were 4.4±4.6 ischemic episodes per 48 hours in the placebo group patients during AECG monitoring (Table 2). The average heart rate was 75.3±11.9 beats per minute, and there were 3.6±4.2 ischemic episodes per 48 hours in the atenolol group patients. The average duration of AECG ischemia was 36.6±4.1 minutes per 48 hours in the placebo group patients and 30.0±3.3 minutes per 48 hours in the atenolol group patients. None of these AECG values at baseline were significantly different comparing placebo and atenolol groups.

**Table 1. Demographic and Other Pertinent Data at Baseline**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=154)</th>
<th>Atenolol (n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>64±8.7</td>
<td>64±8.4</td>
</tr>
<tr>
<td>Age, % ≥65 y</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>Male</td>
<td>84</td>
<td>90</td>
</tr>
<tr>
<td>Caucasian</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Symptomatic*</td>
<td>49</td>
<td>50</td>
</tr>
<tr>
<td>Nitrates continued</td>
<td>32</td>
<td>38</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>75</td>
<td>62</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26</td>
<td>34</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Smoking (active)</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>139±17</td>
<td>137±18</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>81±10</td>
<td>79±10</td>
</tr>
<tr>
<td>HR, beats per minute</td>
<td>74±12</td>
<td>74±11</td>
</tr>
<tr>
<td>Exercise test results at onset ischemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats per minute</td>
<td>127±17</td>
<td>126±17</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>171±26</td>
<td>168±27</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>83±12</td>
<td>83±13</td>
</tr>
<tr>
<td>Exercise time, min</td>
<td>4.2±2.3</td>
<td>4.5±2.2</td>
</tr>
</tbody>
</table>

All data represent % of patients with characteristic unless otherwise noted. MI indicates myocardial infarction; CABG, coronary artery bypass grafting; BP, blood pressure; and HR, heart rate.

*Reported symptoms during qualifying exercise test, ambulatory electrocardiogram monitoring, or nitroglycerin administration.
TABLE 2. Comparison of Baseline and 4-Week Ambulatory Electrocardiogram Monitoring Data (Mean±SD)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Atenolol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>4 Weeks</strong></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>Average heart rate, beats per minute</td>
<td>75.1±12.9</td>
<td>74.9±11.9</td>
</tr>
<tr>
<td>No. of ischemic episodes/48 h</td>
<td>4.4±4.6</td>
<td>3.1±6.0</td>
</tr>
<tr>
<td>Average duration of ischemia, min/48 h</td>
<td>36.6±4.1</td>
<td>30.0±5.5</td>
</tr>
<tr>
<td>Patients with ischemia, %</td>
<td>100%</td>
<td>61</td>
</tr>
</tbody>
</table>

**Primary Outcome**

During follow-up, unfavorable outcome events occurred in 56 patients as event-free survival was significantly increased (P=.0066, log rank Kaplan-Meier) in the atenolol group (Figure). The duration of follow-up averaged 10.4 months and was not significantly different comparing placebo and atenolol groups. Mean time to onset of first event was 120 days in the atenolol group and 79 days in the placebo group. Thirty-nine of 154 (25%) patients assigned to placebo and 17 of 152 (11%, P<.001) patients assigned to atenolol experienced events (Table 3). The relative risk (RR) for adverse outcome associated with atenolol treatment was 0.44, with 95% confidence intervals (CI) of 0.26 to 0.75 (P=.001). The probability of serious events such as death, nonfatal myocardial infarction, resuscitation from VT/VF, or hospitalization for unstable angina showed a nonsignificant trend to reduction in atenolol-treated patients of similar magnitude (RR, 0.55; 95% CI, 0.22 to 1.33; P=.175) (Table 3). Using the commonly accepted definition of unstable angina (angina at rest, usually prolonged; recent onset <2 months; or recent acceleration to effect a change of one class),30 17 patients in the accelerated angina group (11 placebo and 6 atenolol) would be considered to have unstable angina. Thus, using the less restricted definition, 17 placebo-assigned and 10 atenolol-assigned patients developed unstable angina, and the probability of serious events noted above using the common definition of unstable angina was RR, 0.56; 95% CI, 0.29 to 1.03; P=.06.

The possible role of other anti-ischemic therapy was also considered. Overall, there were 38 events in the 210 patients taking aspirin (18%) and 18 (19%) in the 96 patients not taking aspirin. Among the placebo- and atenolol-assigned patients, there were no significant differences in frequency of events whether or not they took aspirin. Overall, there were 19 events in the 105 patients taking long-acting nitrates (18%) and 37 (18%) events in the 201 not taking nitrates. Among the placebo- and atenolol-assigned patients, there were no significant differences in frequency of events whether or not they took long-acting nitrates.

**Other Assessments of Treatment Effect**

Average heart rate decreased significantly with treatment in the atenolol group (75.3±11.9 to 63.2±9.8 beats per minute, P<.0001) but was unchanged in the placebo group (75.1±12.9 to 74.9±11.9 beats per minute, P=.87) (Table 2). In atenolol-treated patients, ischemia on AECG at 4 weeks was significantly reduced in number of episodes (3.6±4.2 to 1.7±4.6, P<.0001), duration (30.0±3.3 to 16.4±6.7 minutes per 48 hours, P<.001), and occurrence (Table 2). There were no significant changes in either the number or duration of ischemic episodes in the placebo group. Differences between the placebo- and atenolol-treated groups' responses at 4 weeks were highly significant when 61% of placebo patients and 40% of atenolol patients (P=.002) had ischemia. Although the data were incomplete because the study was stopped early, the 26- and 52-week AECG results paralleled those obtained at 4 weeks. At 26 weeks, 54% of placebo and only 32% (P<.001) of atenolol patients had ischemia. At 52 weeks, 60% of

Event-free survival: Kaplan-Meier curves comparing the cumulative probabilities of not experiencing an adverse event during follow-up for patients with ambulatory electrocardiogram-monitored silent ischemia randomized to atenolol (upper curve) and placebo (lower curve).
placebo and 42% of atenolol patients had ischemia (P<.001).

Among variables summarized in Tables 1 and 2 and treatment, univariate and multivariate correlates associated with event-free survival at 1 year are listed in Table 4. The most powerful correlate of event-free survival was absence of ischemia at 4 weeks. Other significant factors were age and atenolol assignment. The relation with age was complex; the youngest (<60 years old) and oldest (>70 years old) groups of patients had higher event rates (27% and 21.3%, respectively) compared with patients who were 60 to 69 years old (event rate, 17%). Trends for favorable outcome also were noted for lower diastolic blood pressure and less ischemia at baseline.

Tolerance and Adverse Reactions

In the placebo group 19 patients were down titrated to 50 mg and in the atenolol group 36 patients were down titrated to 50 mg. Thus, 116 patients in the atenolol group took the full 100-mg dose. The proportions of patients with reactions thought to be treatment related were not significantly different comparing the two treatment groups with the exception of bradycardia, which occurred in 6.6% of atenolol-treated patients and none of the placebo-treated patients (P=.001).

Discussion

Patients with CAD who have similar clinical findings can be stratified into high-risk and low-risk groups for adverse outcomes based on the presence of daily life ischemia.4,22 Recently, one small nonrandomized study suggested that medical therapy–related suppression of asymptomatic ischemia, detected by exercise radionuclide angiogram, was associated with improved outcome.31 In another larger but also uncontrolled study, 200 patients who were receiving $\beta$-blockers, calcium blockers, or nitrates were monitored with and without medications and then followed for 1 to 5 years.22 The authors concluded that the response of ST-segment depression on ambulatory monitoring to anti-ischemic medication was predictive of long-term cardiac risk.22 However, data from controlled trials are lacking in determination of whether treatment of patients identified with ischemia during daily life is associated with a reduction in adverse outcomes.

The results of this study suggest that treatment of minimally symptomatic patients who have asymptomatic daily life ischemia with a $\beta$-adrenergic blocker reduces risk of adverse outcomes (Table 3). Benefit resulted from a reduction in risk of occurrence of a combination (primary outcome variable) of ischemia-related cardiac events, (ie, death, resuscitation from VT/VF, myocardial infarction).
dial infarction, hospitalization for unstable angina, aggravation of angina requiring known therapy, and need for revascularization). When a common definition for unstable angina was used, the benefit trend was extended to reduction in risk of serious events (ie, death, resuscitation from VT/VF, myocardial infarction, or unstable angina). The β-blocker also significantly reduced the frequency, duration, and occurrence of daily life ischemia. The univariate and multivariate correlates of favorable outcome at 1 year identified absence of ischemia at week 4, age, and atenolol assignment as making a separate significant contribution to favorable outcome at 1 year (Table 4). Trends were noted for lower diastolic blood pressure and shorter duration of ischemia at baseline.

The reduction in daily life ischemia with atenolol observed in this study was similar in magnitude to that reported in trials that lasted only a few weeks and were of small sample size.28,29,31-35 The results of all of these studies show that atenolol in the dose used in the present study is effective in reducing AECG-monitored ischemia over the short term. The present trial results extend this finding over a 52-week period. Furthermore, the results suggest that asymptomatic and minimally symptomatic patients with CAD, abnormal stress tests, and daily life silent ischemia may have improved event-free survival with long-term β-blocker therapy.

We caution overextension of the results of this trial until the results are confirmed in other ongoing trials. There are several limitations to this study that are worthy of discussion. First, the sample size was relatively small and the duration of follow-up was only 1 year. Clearly, larger groups of patients need to be evaluated over longer periods of time. This study, however, provides new evidence suggesting a link between treatment of patients with AECG-monitored ischemia and reduction in AECG-monitored ischemia with a beneficial outcome effect. Second, the project was not designed to screen the totally asymptomatic population, and all of the patients had previously presented with CAD, so these results should not be extrapolated to the general population of truly asymptomatic subjects. Third, it would have been useful to know if increasing the dose of active therapy or adding another drug in patients with persistent AECG-monitored ischemia had an additional effect on ischemia and outcome. While this problem was considered, the consensus was that it would make the protocol extremely complex for a minimally symptomatic group of patients. Modification of the protocol to access stepwise changes in dose or to add another drug would be likely to have a negative influence on recruitment and adherence. Accordingly, a single drug at a dose shown to be effective for AECG-monitored ischemia in prior studies was chosen.35 Finally, demonstration of clear benefit on survival and myocardial infarction will require a much larger sample size than this trial to detect a treatment effect. A definitive trial probably will require a sample size of more than 5000 patients to detect treatment effects on survival. Such a trial could also be designed to evaluate the impact of anti-ischemic therapy in a variety of subgroups such as women and the elderly.

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Appendix

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